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14. ABSTRACT

The purpose of the study is to evaluate the efficacy of an exercise training augmentation for cognitive training intervention to improve memory performance in older Veterans with a diagnosis of amnestic Mild Cognitive Impairment (aMCI). The investigators hope to learn if a combination of aerobic and resistance exercise program will augment an already established efficacious treatment for persons with aMCI. Currently, the study has successfully obtained continuing review approval from Stanford University's IRB, VA Palo Alto's Research and Development Committee, and approval from the U.S. Army Medical Research and Material Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO). The study has successfully randomized five participants, all of whom are currently in the exercise phase of the study. The data collection phase of the study has also begun with the randomization of participants. As the study is currently ongoing and in the data collection phase, we do not have results to report.

15. SUBJECT TERMS
Cognitive training; Veterans; Mild Cognitive Impairment; physical exercise; intervention; older adults

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Introduction

The graying of our Veteran population presents the VA with an increasingly large number of patients experiencing cognitive impairment, such as amnestic Mild Cognitive Impairment (aMCI). Persons with aMCI have a significantly greater risk of developing dementia than persons without cognitive impairment. We address the need to improve cognition and quality of life in Veterans with aMCI through a two-year, randomized controlled trial. This is a two-phase trial: 1) an exercise phase and 2) a cognitive training program. The exercise phase will be either a combined aerobic and resistance exercise program or a stretching exercise program. Several possibilities exist as to how physical activity impacts cognition. For example, physical activity both increases cardiorespiratory fitness and also reduces the rate and severity of several vascular risk factors for cognitive impairment such as hypertension, obesity, and type II diabetes mellitus [1, 2; 3; 4]. Hence, it may be that by improving cardiovascular health and reducing vascular risk factors associated with cognitive impairment, physical activity is able to delay or prevent cognitive impairment. The investigators hope to learn if a combination of aerobic and resistance exercise program will augment an already established efficacious treatment for persons with aMCI. Participants will attend thrice-weekly group exercise sessions at the VA Palo Alto Health Care System (VAPAHCS) for two months and then transition to a four-month long home-based exercise program. After completion of the exercise program, all participants will attend ten two-hour classroom-based cognitive training at VAPAHCS. The current study will evaluate the efficacy of an exercise training augmentation for cognitive training intervention to improve memory performance in Veterans with a diagnosis of amnestic Mild Cognitive Impairment (aMCI).

Body

The study is currently in the Data Collection Phase. The primary goal of this phase is the successful recruitment and randomization of participants into the trial. This is accomplished through a diverse, multi-modal recruitment plan. One primary form of recruitment has been through the review of electronic medical records at the VAPAHCS. During our initial approval process, we obtained a HIPPA waiver and appropriate approvals to screen using CPRS (VA's Electronic medical record). Study staff received approval from providers to review clinics for potential participants. These clinics include the Geriatric Memory Clinic, VA Outpatient Neuropsychology Service, Stanford/VA Alzheimer's Research Center, and the Mental Illness Research, Education, and Clinical Center. Once potential participants are identified, study staff sends an IRB approved letter from the treating provider to the veteran about the study. This letter includes a contact card so that the veteran would need to "opt-in" to be contacted by study staff regarding a phone screen.

A second mode of recruitment has been through print and online media. Study staff have distributed flyers throughout the VAPAHCS and it's Community Based Outpatient Clinics (CBOCs) as well as the Vet Centers in the area. Flyers and brochures have also been posted at over 95 places in the community including but not limited to senior centers, Veterans of Foreign Wars USAs (VFWs), and libraries. The flyers were provided by the Medical Media at the VA Palo Alto at no cost to the project. We have also placed recurring advertisements in two local newsletters, each of which is widely distributed to older adults in the Bay Area. We have utilized online resources to list the study on clinicaltrials.gov and the list of clinical trials available through the Alzheimer's Association (www.alz.org). Information regarding the study has been placed on the VA Palo Alto's Facebook page as well as the weekly newsletter distributed to staff.

Most recently we expanded our recruitment to those veterans outside of the VA health care system. By collaborating with a local marketing company, we developed study postcards to be distributed across the Bay Area. The result of this collaboration was the mass mailings of our study postcards to veterans across Santa Clara and San Mateo County. Over 5,000 postcards were mailed out to veterans aged 65-85 in Santa Clara county and 3,000 veterans aged 65-85 in San Mateo County. This recruitment method has been quite successful as we have been able to reach thousands of veterans that may not otherwise have heard about the

opportunity of the study. We will continue this recruitment method by targeting Alameda and Contra Costa Counties in the upcoming weeks.

A third aim in the recruitment plan is community outreach. Study staff has given 13 informational and recruitment talks throughout the greater Bay Area. These talks have been at a variety of facilities including: senior centers, professional conferences, veteran's fairs, wellness fairs, senior centers, and independent living facilities. Over 600 older adults have attended these talks. Study staff is continually searching for opportunities throughout the Bay Area to discuss the study with older adults and those who work with older adults.

The fourth arm of the recruitment plan is provider referral. Study staff has worked to educate providers in neurology, primary care, neuropsychology, psychiatry, and psychology about the study and the inclusion / exclusion criteria. We have successfully established partnerships with providers in these clinics and receive participant referrals from them.

From September 27, 2013 to September 26, 2014 we have pre-screened 699 individuals through electronic medical review. Those selected for review were through VA clinics, provider referral, or self-referral. Of those 699 individuals that have been pre-screened, 217 were contacted and 29 completed phone screen interviews. The most frequent reasons individuals were excluded from the pre-screening list were exclusionary codes E02 (14% N=98), E03 (12% N=90) and E10 (14% N=99). Exclusionary code E02 indicates participant has a diagnosis of dementia. E03 exclusionary code indicates the participant has a history of a neurological disorder. E10 indicates the participant is not in between the ages of 50 and 90. Combined, 287 (41%) individuals were excluded due to a diagnosis of dementia, a history of a neurological disorder, or they did not meet the age criteria. The remaining was excluded for reasons including: acute illness or unstable chronic illness, current severe psychiatric disorder, current severe cardiac disease, orthopedic or musculoskeletal problems, morbid obesity, vision loss, or deceased.

From September 27, 2013 to September 26, 2014 we have phone screened a total of 93 potential participants. Of those 93 veterans who completed the phone screen interview, 60 participants were consented by study staff and completed screening measures at VA Palo Alto. Of those 60 participants who were consented and completed screening measures, 26 have been randomized to study treatment arms (Combined Aerobic and Resistance Exercise: 15 participant; Stretching Exercise: 11 participants). Currently there are 12 veterans that have enrolled since.

Key Research Accomplishments

- Initiation of Data Collection Phase
    - Prescreened 699 individuals
    - Phone screened 93 individuals
    - Screened 60 individuals
    - Randomized 26 participants
        - 15 randomized in the combined aerobic and resistance exercise program
        - 11 randomized in the stretching exercise program
- Obtained most recent continuing review approval
        - VA Palo Alto's Research and Development Committee 23-Jan-2014
        - Stanford University IRB 11-Jun-2014
        - USMRMC Office of Research Protections 6-Feb-2014

Reportable Outcomes

At this time of this report 26 Veterans that had been randomized to treatment. Of those 26, 10 veterans have successfully completed the eight month intervention. Below we highlight preliminary data comparing the two groups of interest on the primary and secondary outcome measures.

Figure 1. Delayed Recall of Word List

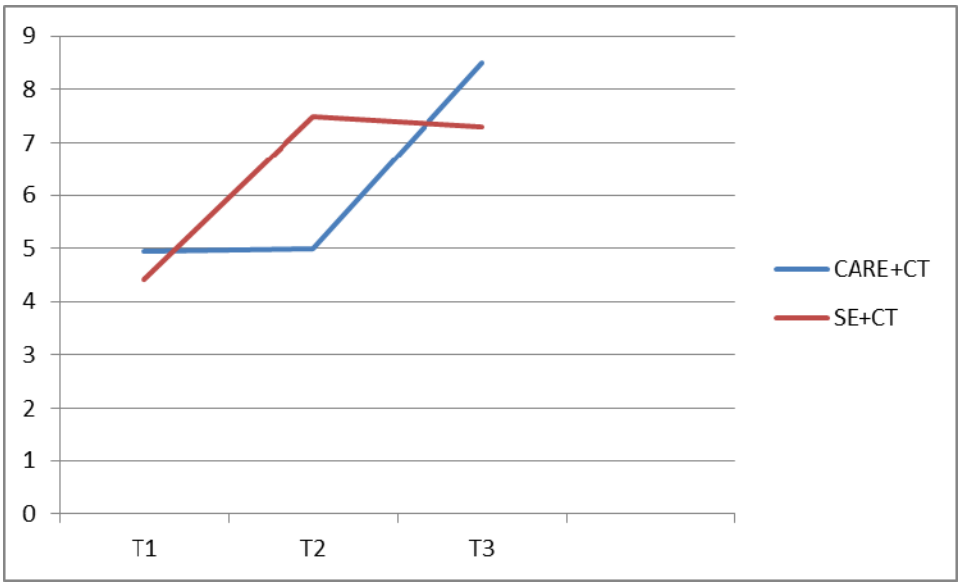


Figure 2. Names and Faces

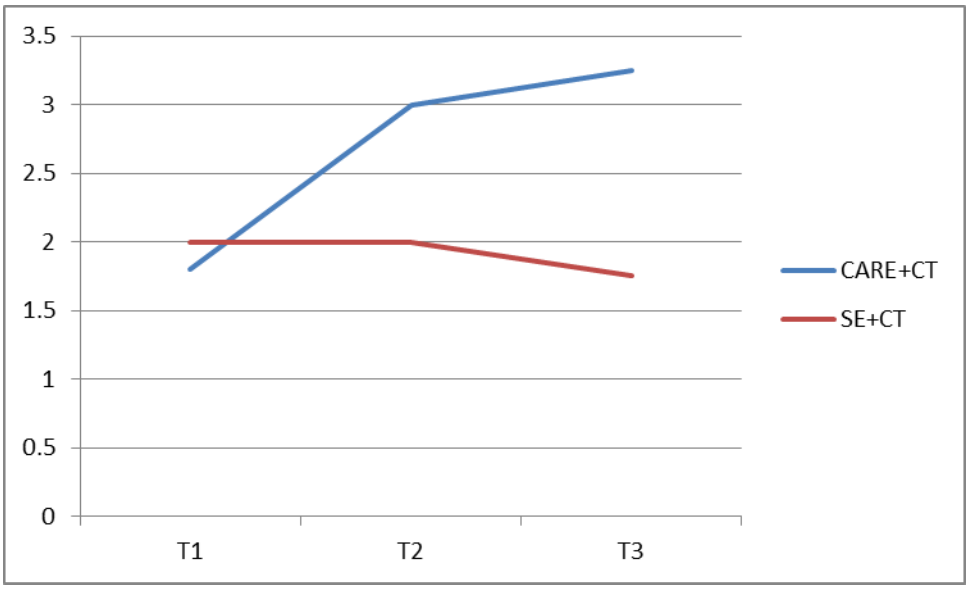


Figure 3. Geriatric Depression

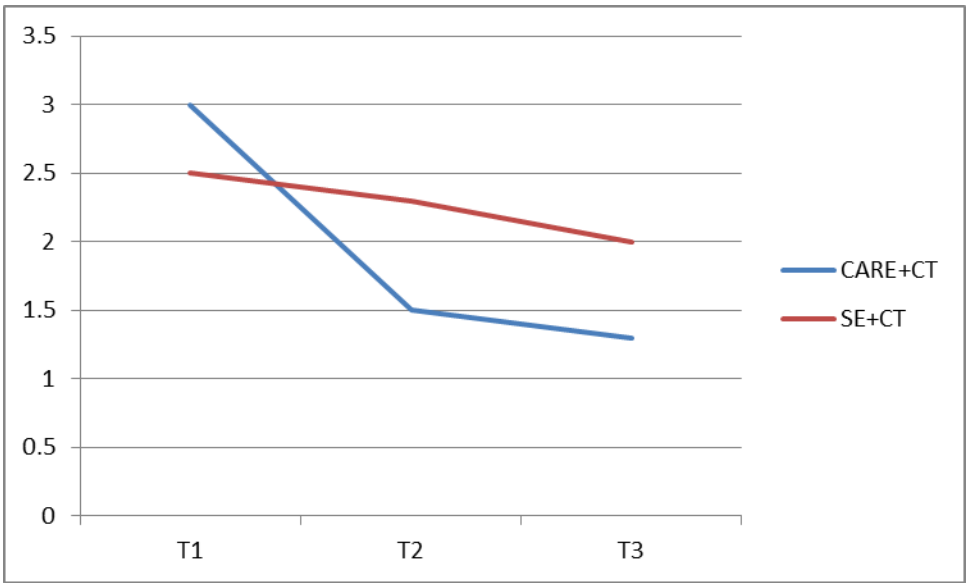


Figure 4. Quality of Life: Positive

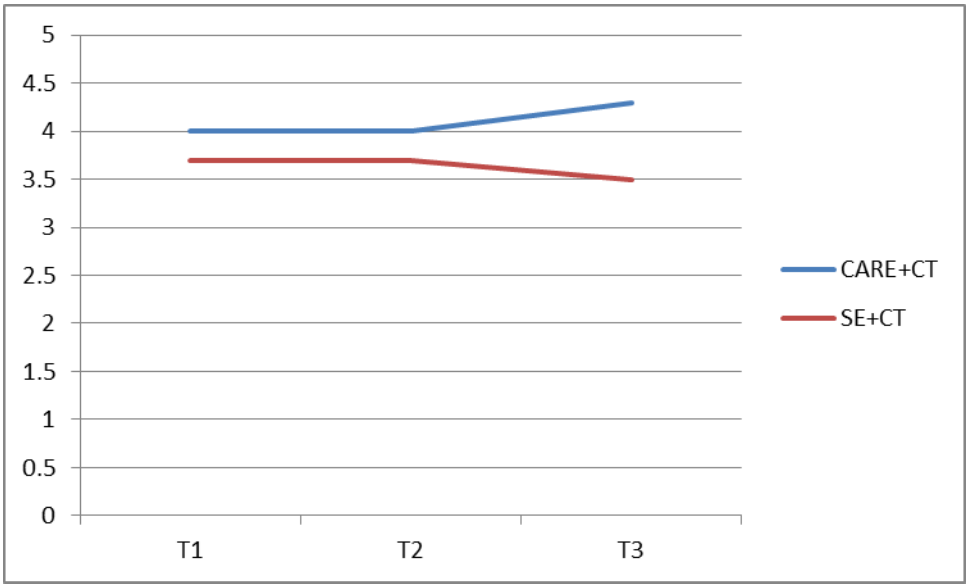


Figure. 5 Quality of Life: Negative

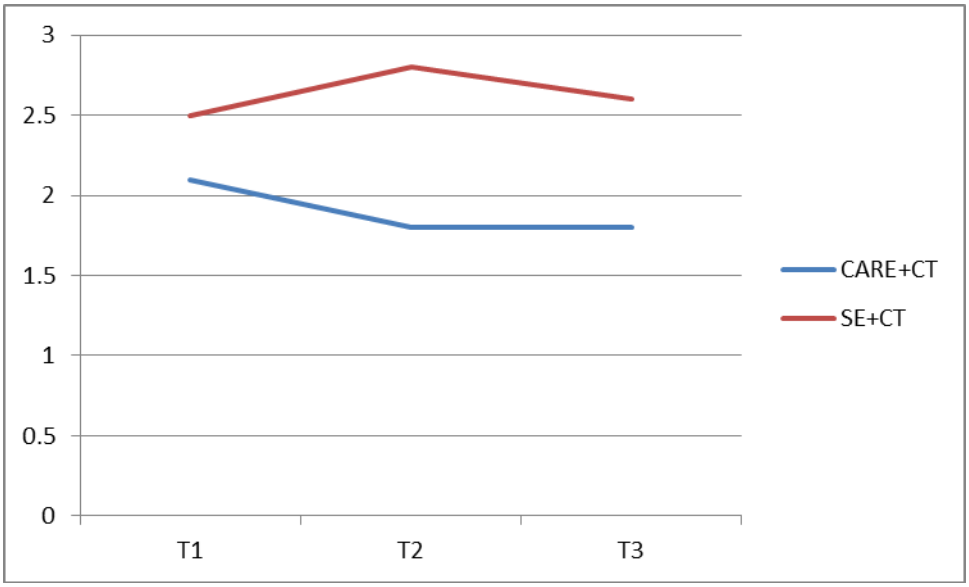
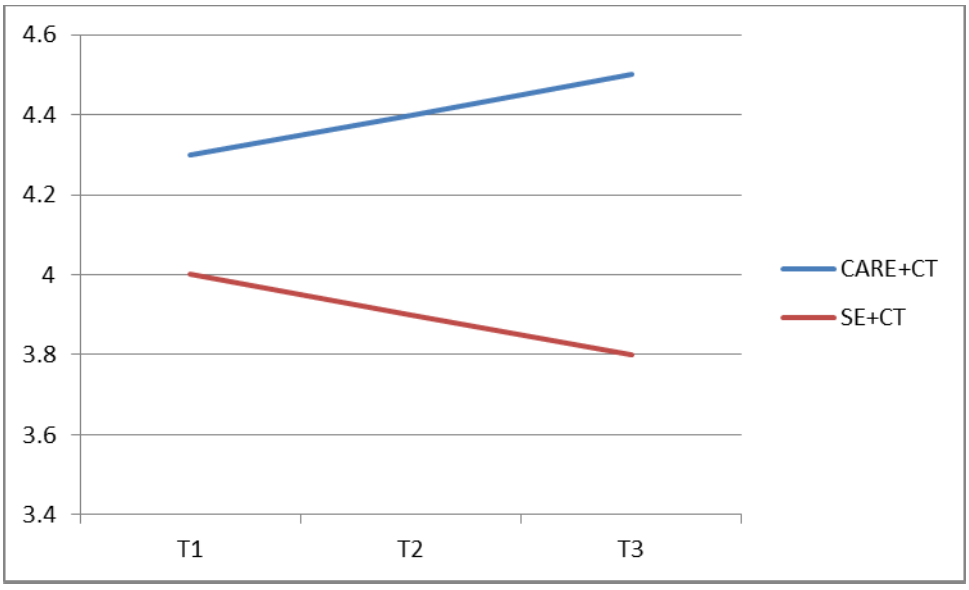


Figure 6: Quality of Life: Self-Esteem



Conclusions

As of September 26, 2014 the study has successfully continued the Data Collection phase and all the associated tasks (i.e., obtaining of regulatory approvals, purchasing of necessary equipment, and hiring of staff). To date, we have pre-screened almost 700 potential participants. Of that number, 93 older adults have completed phone screens. Of those 93 older adults, 60 participants have been screened and 26 were then randomized. Since then there are currently 12 veterans who have been enrolled.

To enhance our recruitment flow we began to send out mass mailings to veterans across the Bay Area in Santa Clara and San Mateo County. Postcards advertising our study were sent out to thousands of veterans' homes as an opportunity to reach as many veterans as possible. This recruitment method has been quite successful; we were able to reach veterans who may otherwise have not had the opportunity to hear about our study. We will continue this recruitment method in the upcoming weeks by targeting Alameda and Contra Costa Counties.

At present there are no pharmacological interventions with demonstrated efficacy for the improvement of cognition related to MCI, thus the results of this research have the potential to make a great impact on the lives of older veterans and civilians alike. Veterans, in particular, experience a larger burden of psychiatric and medical illnesses than non-Veterans, which may place them at higher risk for developing cognitive decline.

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Supplemental Data

Table 1. Phone Screen Failures

Exclusionary code	Phone Screen Fails (N=33)	Exclusionary code description
E01	6% (N=2)	Current severe psychiatric disorder
E03	3% (N=1)	History of neurological disorder
E06	3% (N=1)	Orthopedic or musculoskeletal problems
E10	6% (N=2)	Not in between the ages of 50-90
E15	3% (N=1)	Unwilling to participate for 8 months
E_Other	78% (N=26)	Participants did not follow up or return voice mails for further screening visits.

Table 2. In House Screen Failures

Exclusionary code	Screen Fails (N=34)	Exclusionary code description
E01	5% (N=2)	Current severe psychiatric disorder
E02	2% (N=1)	Diagnosis of dementia
E03	2% (N=1)	History of neurological disorder
E05	2% (N=1)	Current severe cardiac disease
E06	2% (N=1)	Orthopedic or musculoskeletal problems
E07	2% (N=1)	Morbid obesity (BMI > 39)
E11	58% (N=20)	Did not have a diagnosis of aMCI
E_Other	5% (N=2)	One participant would like to be contacted in Spring 2014 and the other did not follow up with voice mail for further screening.

Table 3. List of Exclusionary Criteria

Exclusionary Criteria	
Screen Code	**Criteria**
E01	Current severe psychiatric disorder, such as Bipolar I, Schizophrenia, or Major Depressive Disorder, determined by the Mini International Neuropsychiatric Interview (MINI).
E02	Diagnosis of dementia, CDR > 0.5; modified Hachinski score ≥ 4; Blessed Orientation Memory Concentration task (BOMC) > 10, or delirium (those with scores indicative of dementia will be referred to the ARC for a full diagnostic work-up).
E03	History of neurological disorder (e.g., multiple sclerosis, seizure disorder, stroke, history of transient ischemic attacks) or systemic illness affecting CNS function (e.g., liver failure, kidney failure, congestive heart failure, systemic cancer)
E04	Acute illness or unstable chronic illness, e.g., history of severe liver disease (cirrhosis, esophageal varices, ascites, portal hypertension, hepatic encephalopathy).
E05	Current severe cardiac disease (e.g., uncontrolled atrial fibrillation, defined as mean 24 hour heart rate > 85 beats/min, or 24 hour maximal ventricular rate >150 beats/min; uncontrolled ventricular arrhythmias, defined as recurrent ventricular tachycardia > 3 beats in succession, or 24 hour PVC count > 20%; active pericarditis or myocarditis; Class III/IV heart failure and / or ejection fraction < 20%; thrombophlebitis; pulmonary disease with a drop in O2 Sat with exercise to 90% without oxygen; embolism within past 6 months).
E06	Inability to participate in an exercise stress test or inability to exercise consistently because of orthopedic or musculoskeletal problems
E07	Morbid obesity (BMI > 39).
E08	Inability to read, verbalize understanding and voluntarily sign the Informed Consent. Veterans meeting any of these exclusion criteria will be excluded from all aspects of this project.
E09	Not a veteran
E10	Not in between the ages of 50-90
E11	Did not have a diagnosis of aMCI
E12	Did not have an available informant to document cognitive impairment and functional status
E13	Did not have sufficient visual and auditory acuity to allow neuropsychological testing
E15	Did not have willingness to participate in exercise training + cognitive training program for 8 months.
E16	Did not have approval of primary provider to participate in an exercise trial.
E17	Refusal to sign the consent and or HIPAA form